REMARKS

Claims 1-10, 13-22 were pending. Claims 1-9 and 17-22 were previously withdrawn by the Examiner. . Claim 10 has been amended to further specify the molecular entities imparting diagnostic utility. Support is found throughout the specification, including at pages 10-12 and original claim 6.

Information Disclosure Statements

Applicants thank the Examiner for considering the references in the Information Disclosure Statements filed on July 7, 1008.

Drawings

The objection to the drawings as allegedly failing to show the migration described in the specification was maintained. The Examiner found that Figure 3 as originally filed was extremely vague and that "the 'migration' in lanes 2, 4, 5 and 6 cannot be determined." While Applicants submit that Figure 3 as originally filed is sufficient and is not vague, solely to expedite prosecution, Applicants are submitting Replacement Drawings. In the Replacement Drawings, Figure 3 has been replaced with a more legible picture of the electrophoresis of rFab preparations before and after exhaustive alkylation with Compound D of Example 2. The electrophoresis was done as described in Example 5. This Replacement Figure 3 clearly shows the migration in all 6 lanes. Thus, the reduction in migration distance that follows reaction with Compound D is apparent. Specifically, in each case the Fab preparations conjugated with Compound D (lanes 2, 4 and 6) showed the same reduction in migration distance towards the cathode when compared with the corresponding unconjugated Fab preparation (lanes 1, 3 and 5 respectively). The reduction in migration distance that follows conjugation with Compound D

confirms the attachment of a definite number of negatively charged groups and thus the controlled stoichiometry of the claimed method.

The remaining Replacement Figures are identical to the originally submitted figures. Applicants submit that the Replacement Figures include all structural details essential for a proper understanding of the invention and are in full compliance with37 C.F.R 1.83(a).

Rejections Under 35 U.S.C. § 112

Applicants are grateful for the withdrawal of these rejections.

Rejections Under 35 U.S.C. § 102

Applicants are grateful for the withdrawal of the rejection of Claim 10 under 35 U.S.C. 102 for alleged anticipation by Hansen et al WO 91/04056 ("Hansen").

The rejection of claims 10-13 and 15 under 35 U.S.C. 102 for alleged anticipation by Maurer et al WO 02/056907 ("Maurer") was maintained. The Examiner asserts that the Qβ capsid protein disclosed by Maurer "appears to be a molecular entity which imparts diagnostic utility as defined in the specification, e.g., a hapten." P. 6. The Examiner also asserts that Maurer discloses the claimed method including an overlapping TCEP concentration.

Applicants respectfully traverse. As an initial matter, the claims require a chemical conjugate between an immunoglobulin Fab fragment and molecular entities imparting diagnostic utility. "Diagnostic utility" is understood by the skilled artisan to refer to a moiety which provides diagnostic information, such as for example, a signal from a detectable label, and is distinguished in the specification from therapeutic utility, which , provides some therapeutic benefit. For example, the specification explains:

> Those conjugates in which the linked diagnostic or therapeutic molecule does not interfere with the capability of binding to the target antigen are able to transport and thus target the molecule to antigen-bearing cells and tissues, where it can

> exert it sineteded purpose, such as, for example, **diagnostic signal production** or **therapeutic cell killing**.

p. 1, lines 18-22 (emphasis added). Furthermore, the currently amended claims specify that the moiety imparting diagnostic utility is selected from the group consisting of derivatives of chelating agents for, or chelates of, radionuclides, paramagnetic metal ions or luminescent metal ions, a chromophoric fluorescent or a phosphorescent molecule, a lipophilic chain bearing molecular entity incorporated into liposomes, phospholipid-stabilized microbubbles, triglyceride- or polymer-based microspheres, and microballooons. The skilled artisan reading this list would immediately understand that a hapten is of therapeutic utility, while the agents which provide a detectable label or signal, such as , for example, the chelating agents, chromophoric fluorescent or phosphorescent molecules, and the entities detectable by ultrasound (e.g. microbubbles, etc) are of diagnostic utility. Indeed, the hapten disclosed in Maurer is stated to be useful for preparing a vaccine, which one skilled in the art would understand to be of therapeutic utility. Thus, contrary to the Examiner's assertion, Maurer does not disclose a conjugate between a Fab and molecular entities imparting diagnostic utility as required by the claim.

In summary, Maurer fails to teach all of the limitations of claims 10-13 and 15; thus these claims are not anticipated.

Rejections Under 35 U.S.C. § 103

The rejection of claims 14 and 16 under 35 U.S.C. for alleged obviousness over Maurer as evidenced by Cruse and Lewis, Illustrated Dictionary of Immunology, Boca Raton, FL 1995 ("Cruse and Lewis") was maintained. The examiner asserts that Maurer teaches a method of coupling Fab fragments to Qβ capsid proteins using, inter alia, concentrations of TCEP which

overlap with the range in the instant claims. Moreover, the Examiner asserts that Maurer's "method of conjugating the protein to the Fab fragment appears to use a controlled stiochiometric molar ratio of 1 to 1..." (p. 9) , relying on Exhibit 1, which states:

Exhibit I

Conversion of mg/mL to μM, e.g. μmol/L

(2.5mg/mL) X (1mmol/47,000mg) X (1000mL/1L)= .053 mmol/L or 53μM

"Thus, while the Examiner does not dispute that the reaction mixture produces a complex mixture of products and reactants, the Examiner recognizes that the product, e.g., average molecular weight of approximately 40Kd shown by the arrow in Figure 21, is still produced using the method taught by Maurer." P 9. Applicants respectfully traverse.

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396 (2207) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." MPEP Section 2143.

"The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." 83 UDPQ2d at 1395 and MPEP Section 2143. Further, a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. (MPEP 2144.09).

Applicants respectfully assert that the combination of the cited references does

not teach or suggest all of the claim limitations and that the claimed compounds possess unexpectedly superior properties. Therefore, applicants respectfully traverse the § 103 rejection.

As explained supra, Maurer fails to disclose a process for preparing a chemical conjugate between an immunoglobulin Fab fragment and a diagnostic moiety as defined by the claims. Maurer,is directed to producing conjugates for vaccines, a therapeutic utilty, and neither teaches nor suggests diagnostic conjugates. This deficiency is not remedied by the secondary reference.

Additionally, unlike Maurer, the present process provides for a diagnostic entity with a controlled stoichiometry of conjugation (e.g. the stoichiometric molar ratio of molecular entity to Fab fragment in the conjuagates is in the range from 0.95 to 1.05 or in the range from 1.95 to 2.05).

Being able to control the stoichiometric ratio during conjugation is of the utmost importance as it allows for chemically defined conjugated diagnostic compounds, in comparison to the rather complex and poorly defined mixtures of conjugated compounds obtained according to the process of Maurer, wherein each of the conjugates in the obtained mixture may have its own stoichiometry of substitution and thus, the claimed stoichiometric ratios cannot be achieved.

Indeed, Example 16 of Maurer establishes that each of the successful couplings between the Fab fragment and the protein (see lanes 5-8 and lanes 10-12 of figure 21) is part of a very complex mixture in which only a portion includes the desired conjugate (with average MW of 40 kDa, shown by an arrow in figure 21). Indeed, these mixtures can include significant amounts of uncoupled Fab fragments (MW 25kDa) and other undesired compounds, highlighting the inability of the Maurer method to control stoichiometry, and requiring extensive, expensive and impractical separation methods to isolate the derivative of interest from the complex mixture

containing it. Moreover, this lack of stoichiometric control occurs regardless of the reducing agent used (TCEP or DTT) and regardless of the concentrations used – in each case Maurer wound up with a complex mixture resulting from an inability to control the stoichiometry. See e.g., Fig. 21.

In contrast, in the present invention, the claimed method unexpectedly yields controlled stoichiometry of substitution through the selective and quantitative reduction of the inter-chain disulfide bond of a Fab fragment using TCEP so as to provide for two sulfhydryl groups to be then reacted with the diagnostic moiety or moieties bearing free sulfhydryl reactive groups. As shown in lanes 2, 4 and 6 of Fig. 3, homogeneous products are formed, from a pre-determined, controlled stoichiometry of conjugation that greatly reduces any impurities and allows the desired product to be obtained from a much simpler mixture. See, e.g. p 16, lines 8-23. Neither the method nor the advantages are taught or suggested by Maurer.

The secondary reference, Cruse and Lewis, fails to remedy the deficiencies of Maurer. Indeed, it was cited by the Examiner for the molecular weight of the Fab of Maurer and fails to teach or suggest the claimed methods. Whether taken alone or together, the cited references fail to teach or suggest the claimed methods, which provide diagnostic conjugates of controlled stiochiometry and specified stoichiometric ratio through the selective and quantitative reduction of the inter-chain disulfide bond of a Fab fragment using TCEP at concentrations ranging from 0.1 to 10 mM.

In view of the present amendments and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

No fee is believed to be necessary in connection with the filing of this

Amendment and Response to Restriction Requirement. However, if any additional fee is necessary, applicant hereby authorizes such fee to be charged to Deposit Account No. 50-2168.

Respectfully submitted,

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